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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,249	11/17/2000	Susanne Dagmar Pippig	4-31192/CIP	7928

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EXAMINER

LOEB, BRONWEN

ART UNIT PAPER NUMBER

1636

DATE MAILED: 02/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/715,249

Applicant(s)

PIPPIG ET AL.

Examiner

Bronwen M. Loeb

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 November 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 4 and 30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 November 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 & 8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

This action is in response to the communication filed 19 November 2001.

Claims 1-30 are pending.

### ***Election/Restrictions***

1. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the search of one group is likely to encompass subject matter pertinent to the patentability of all the groups and that such a search would not be a serious burden. This is not found persuasive because while possibly overlapping, the searches are not coextensive. Searching for nucleic acid sequences encoding a mutated/modified EGFR is not coextensive with a search for nucleic acid sequences encoding a mutated/modified MuSK-R and neither is coextensive with a search of a mutated/modified MuSK-R which is a protein.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 2 and 5-29 are examined only to the extent that they read on a modified EGFR family member.
3. Claims 4 and 30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

### ***Specification***

4. The disclosure is objected to because of the following informalities: two sequence listing were submitted in the as-filed application, one labeled pp.41-50 and

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the other labeled pp.1-19. While the listing labeled pp. 1-19 appears to correspond to the raw sequence listing provided on the computer readable format, it is unclear to which sequence listing the statement of identical content refers.

Appropriate correction is required.

### ***Claim Objections***

5. Claims 2, 3, 6, 16, 17, 22, 27 and 28 are objected to because of the following informalities: Claims 2, 6, 17,22 and 28 are objected to as reciting an unelected invention (MuSK-R). Claim 3 should recite SEQ ID Nos. for the sequences designated EGFR1-I and EGFR1-II. Claim 3 is also objected for reciting "sequence" which is grammatically incorrect; the word should be plural. Claim 16 appears to recite two method steps in step (a); "incorporating....." and "introducing...". Claim 27 is redundant in reciting "a nucleic acid encoding a nucleic acid comprising a DNA sequence" in step a); it would be remedial to amend the claim to recite "a nucleic acid encoding a protein of interest and a protein-tyrosine kinase receptor...".

Appropriate correction is required.

6. Applicant is advised that should claim 9 be found allowable, claim 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 and 5-29 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad. Claims 1 and 16 are drawn to a method of identifying any genetically modified mammalian cells using any mutated EGFR family member having any mutation in both the intracellular and extracellular domain, or in the intracellular domain alone. Claim 20 is drawn to a method of immunoselection of any transduced mammalian cells using any retroviral vector encoding any mutated EGFR family member having any mutation in both the intracellular and extracellular domain, or

in the intracellular domain alone. Claim 27 is drawn to a method of identifying mammalian cells expressing any protein of interest using nucleic acid encoding any mutated EGFR family member having any mutation in both the intracellular and extracellular domain, or in the intracellular domain alone and any protein of interest.

The nature of the invention is a method of producing genetically modified mammalian cells all of which express a mutated EGFR family member. The cells so produced are disclosed solely as having use in gene therapy (p. 25, lines 10-17).

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1<sup>st</sup> paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the transgene. Regarding viral methods for gene delivery, Verma et al indicates that viral vectors have the problem of stimulating undesirable host immune responses (p. 239, col. 3, 3<sup>rd</sup> paragraph). Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2<sup>nd</sup> paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1<sup>st</sup> and 2<sup>nd</sup> paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and

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advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al, p. 33, col. 1, 1<sup>st</sup> paragraph.

The relative skill of those in the art of gene therapy is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support gene therapy applications of the genetically modified cells produced by the claimed methods. The specification discloses no specific therapeutic molecules and diseases to which the genetically modified cells can be applied. There is no direction provided as to how to overcome the obstacle to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression in vivo.

It is also unclear how genetically modified cells expressing a mutated EGFR member alone would provide a therapeutic benefit in gene therapy. If the cells which are modified comprise endogenous EGFR receptors, one would expect that the mutated ones might dimerize with the endogenous receptors, rendering them non-functional or

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perhaps constitutively active. Alternately, the mutated EGFR receptor may compete for ligand, reducing the effectiveness of the endogenous receptor.

No working examples are disclosed which encompass the use of the genetically modified cells for gene therapy.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in any cell type, whether the effect could be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. In modified cells comprising only the mutated EGFR member and not an additional therapeutic polypeptide, one would have to ascertain a use for such cells in gene therapy. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the product of the claimed method.



9. The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-3, 6-15, 17 and 20-29 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in not reciting a step which clearly refers back to the preamble. Specifically, the preamble recites a "genetically modified mammalian cells" however the steps do not lead to genetically modified *mammalian* cells, but rather to genetically modified cells.

Claim 1 is vague and indefinite in reciting "a modification to the intracellular and the extracellular domains". Is it unclear how a single modification can affect two separate domains.

Claim 3 is vague and indefinite in reciting "the sequences designated EGFR1-I and EGFR1-II". The specification does not teach what these specific sequences are, they are not listed in the sequence listing nor are there SEQ ID Nos. for them.

Regarding claims 17, 22 and 28, the phrase "preferably" renders each claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 20 is vague and indefinite as it recites "immunoselection" in the preamble however the method steps lead only to immuno-screening or identifying transduced cells. There is no selection step recited.

Claims 23 and 24 are vague and indefinite in reciting "derived from". The number and nature of derivative steps is unknown.

Claim 27 is vague and indefinite as it is unclear whether both the protein of interest and the protein-tyrosine kinase receptor family member are operatively linked to a single expression control sequence (polycistronic) or if just one or the other is operatively linked to it.

### **Conclusion**

Claims 1-3 and 5-29 are rejected.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.  
Patent Examiner  
Art Unit 1636

February 8, 2002

  
REMY YUCEL, PH.D.  
PRIMARY EXAMINER